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The Patent Office

Cardiff Road
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1. Your reference — 101370-1

2. Patent application number *(The Patent Office will fill in this part)* — 0402277.8

03FEB04 E870177-1 D02934
P01/7700 0.00-0402277.8 NONE

3 FEB 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* — 7822448003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)* — Lucy Clare Padget

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
Global Intellectual Property
P O Box 272
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4GR

Patents ADP number *(if you know it)* — 8179707001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
   See note (d))

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Continuation sheets of this form	
Description	47
Claim *(s)*	3
Abstract	1
Drawing *(s)*	

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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 2/2/2004

12. Name and daytime telephone number of person to contact in the United Kingdom

Shirley Douglas - 01625 510057

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CHEMICAL COMPOUNDS

The invention relates to pyrimidine derivatives, or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, which possess cell-cycle inhibitory activity and are accordingly useful for their anti-cell-proliferation (such as anti-cancer) activity and are therefore useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cell-proliferation effect in a warm-blooded animal such as man.

The cell cycle is fundamental to the survival, regulation and proliferation of cells and is highly regulated to ensure that each step progresses in a timely and orderly manner. The progression of cells through the cell cycle arises from the sequential activation and de-activation of several members of the cyclin-dependent kinase (CDK) family. The activation of CDKs is dependent on their interaction with a family of intracellular proteins called cyclins. Cyclins bind to CDKs and this association is essential for CDK activity (such as CDK1, CDK2, CDK4 and/or CDK6) within the cell. Different cyclins are expressed and degraded at different points in the cell cycle to ensure that activation and inactivation of CDKs occurs in the correct order for progression through the cell cycle.

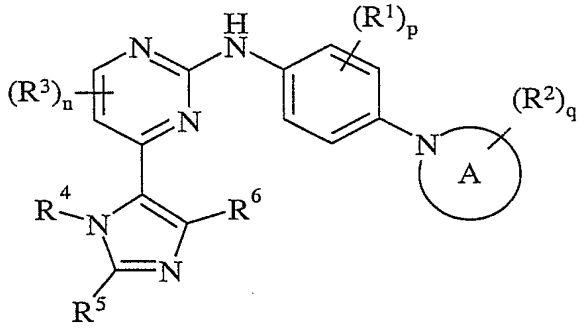
Moreover, CDKs appear to be downstream of a number of oncogene signalling pathways. Deregulation of CDK activity by upregulation of cyclins and/or deletion of endogenous inhibitors appears to be an important axis between mitogenic signalling pathways and proliferation of tumour cells.

Accordingly it has been recognised that an inhibitor of cell cycle kinases, particularly inhibitors of CDK1, CDK2 and/or CDK4 (which operate at the G2/M, G1/S-S-G2/M and G1-S phases respectively) should be of value as an active inhibitor of cell proliferation, such as growth of mammalian cancer cells.

The inhibition of cell cycle kinases is expected to be of value in the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

WO 02/20512, WO 03/076435, WO 03/076436, WO 03/076434 and WO 03/076433 describe certain 2-anilino-4-imidazolylpyrimidine derivatives that inhibit the effect of cell cycle kinases. The present invention is based on the discovery that a novel group of 2-(4-piperazin-1-ylanilino)-4-imidazolylpyrimidines surprisingly inhibit the effects of cell cycle kinases showing activity against CDK1 and CDK2, particularly CDK2, and thus possess anti-cell-proliferation properties. The compounds of the present invention are not specifically disclosed in any of the above applications and we have surprisingly found that these compounds possess beneficial properties in terms of one or more of their pharmacological activity (particularly as compounds which inhibit CDK2) and / or pharmacokinetic, efficacious, metabolic and toxicological profiles that make them particularly suitable for *in vivo* administration to a warm blooded animal, such as man. In particular these compounds show improved physical and metabolic properties compared to those previously disclosed.

Accordingly, the present invention provides a compound of formula (I):



(I)

wherein:

Ring A is a nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom; wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7;

$\mathbf{R^1}$ is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkynyl;

p is 0-4; wherein the values of R^1 may be the same or different;

$\mathbf{R^2}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; wherein R^2

independently may be optionally substituted on carbon by one or more R^8; or R^2 is -NHR^9, -NR^{10}R^{11} or -O-R^{12};

q is 0-2; wherein the values of R^2 maybe the same or different;

R^3 is halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-3}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-3}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl or *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl; wherein R^3 may be independently optionally substituted on carbon by one or more R^{13};

n is 0 to 2, wherein the values of R^3 may be the same or different;

R^4 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or a carbon-linked heterocyclyl; wherein R^4 may be optionally substituted on carbon by one or more R^{14}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15};

R^5 and **R^6** are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-8}cycloalkyl or a 4-7 membered saturated heterocyclic group; wherein R^5 and R^6 independently of each other may be optionally substituted on carbon by one or more R^{16}; and wherein if a 4-7 membered saturated heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

R^7, **R^9**, **R^{10}**, **R^{11}** and **R^{12}** are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, C_{2-6}alkynylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, carbocyclyl, heterocyclyl, carbocyclyl-R^{18}- or heterocyclyl-R^{19}-; wherein R^7, R^9, R^{10}, R^{11} and R^{12} may be independently optionally substituted on carbon by a group selected from R^{20}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by R^{21};

R^{14} and **R^{20}** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy,

C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{1-6}alkyl-R^{22}-, heterocyclylC_{1-6}alkyl-R^{23}-, carbocyclyl-R^{24}- or heterocyclyl-R^{25}-; wherein R^{14} and R^{20} may be optionally substituted on carbon by one or more R^{26}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{27};

R^{18}, **R^{19}**, **R^{22}**, **R^{23}**, **R^{24}**, **R^{25}** are independently selected from -O-, -N(R^{28})-, -C(O)-, -N(R^{29})C(O)-, -C(O)N(R^{30})-, -S(O)$_s$-, -SO_2N(R^{31})- or -N(R^{32})SO_2-; wherein **R^{28}**, **R^{29}**, **R^{30}**, **R^{31}** and **R^{32}** are independently selected from hydrogen or C_{1-6}alkyl and **s** is 0-2;

R^{15}, **R^{17}**, **R^{21}** and **R^{27}** and are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R^{15}, R^{17}, R^{21} and R^{27} independently of each other may be optionally substituted on carbon by on or more R^{33}; and

R^{8}, **R^{13}**, **R^{16}**, **R^{26}** and **R^{33}** are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" and "C_{1-4}alkyl" include methyl, ethyl, propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "carbocyclylC_{1-6}alkyl-R^{20}," includes

carbocyclylmethyl-R^{20}, 1-carbocyclylethyl-R^{20} and 2-carbocyclylethyl-R^{20}. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring nitrogen atom may optionally bear a C_{1-6}alkyl group and form a quaternary compound or a ring nitrogen and/or sulphur atom may be optionally oxidised to form the *N*-oxide and or the S-oxides. Examples and suitable values of the term "heterocyclyl" are morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, isothiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, *N*-methylpyrrolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide and quinoline-*N*-oxide. In one aspect of the invention a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked, a $-CH_2-$ group can optionally be replaced by a -C(O)-and a ring sulphur atom may be optionally oxidised to form the S-oxides.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. Particularly "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl.

A "4-7 membered saturated heterocyclic group" is a saturated monocyclic ring containing 4-7 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and a sulphur atom may be optionally oxidised to form the S-oxides. Examples and suitable values of the term "4-7 membered saturated heterocyclic group" are morpholino, piperidyl, 1,4-dioxanyl, 1,3-dioxolanyl, 1,2-oxathiolanyl,

imidazolidinyl, pyrazolidinyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, homopiperazinyl and tetrahydropyranyl.

Ring A is a "nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom". A "nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom" is a saturated monocyclic ring containing 4-7 atoms linked to the phenyl moiety of formula **(I)** via a nitrogen atom contained in the ring, the ring optionally contains an additional heteroatom selected from nitrogen, sulphur or oxygen, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, and the optional sulphur atom may be optionally oxidised to form the S-oxides.

Examples of "C_{1-3}alkyl" include methyl, ethyl, propyl and isopropyl. An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxy" and "C_{1-3}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" and "C_{1-3}alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2" and "C_{1-3}alkyl$S(O)_a$ wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkyl$S(O)_r$ wherein r is 1 to 2" include methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" and "C_{1-3}alkanoyl" include propionyl and acetyl. Examples of "*N*-C_{1-6}alkylamino" and "*N*-C_{1-3}alkylamino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" and "*N,N*-(C_{1-3}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-6}alkenyl" and "C_{2-3}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" and "C_{2-3}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" and "*N*-(C_{1-3}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$sulphamoyl" and "*N,N*-(C_{1-3}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" and "*N*-(C_{1-3}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" and "*N,N*-(C_{1-3}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C_{3-8}cycloalkyl" are cyclopropyl, cyclobutyl, cyclopropyl and cyclohexyl. Examples of "C_{1-6}alkylsulphonylamino" include methylsulphonylamino, isopropylsulphonylamino and *t*-butylsulphonylamino. Examples of "C_{1-6}alkylsulphonyl" include methylsulphonyl, isopropylsulphonyl and *t*-butylsulphonyl. Examples of

"C_{2-6}alkenylsulphonyl" include vinylsulphonyl, allylsulphonyl and 1-propenylsulphonyl. Examples of "C_{2-6}alkynylsulphonyl" include ethynylsulphonyl, 1-propynylsulphonyl and 2-propynylsulphonyl. Examples of "C_{1-6}alkoxyC_{1-6}alkoxy" include methoxyethoxy, 2-ethoxypropoxy and 2-isopropoxybutoxy. Examples of "C_{1-6}alkoxyC_{1-6}alkoxyC_{1-6}alkoxy" include methoxyethoxymethoxy, 2-ethoxypropoxymethoxy and 3-(2-isopropoxybutoxy)ethoxy.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

An *in vivo* hydrolysable ester of a compound of the formula **(I)** containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula **(I)** containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and

N-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

Some compounds of the formula **(I)** may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess CDK inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula **(I)** that possess CDK inhibitory activity. In particular the skilled reader will appreciate that when R^4 is hydrogen, the imidazole ring as drawn in formula **(I)** may tautomerise.

It is also to be understood that certain compounds of the formula **(I)** can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess CDK inhibitory activity.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Ring A is a nitrogen linked 6 membered saturated ring which optionally contains an additional nitrogen atom; wherein if Ring A contains an nitrogen atom that nitrogen may be optionally substituted by R^7; wherein

R^7 is selected from C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl and C_{2-6}alkenylsulphonyl; wherein R^7 may be optionally substituted on carbon by a group selected from R^{18}; wherein

R^{18} is selected from hydroxy, C_{1-6}alkoxy, C_{1-6}alkanoyloxy and *N,N*-(C_{1-6}alkyl)$_2$amino.

Ring A is morpholino or piperazin-1-yl; wherein if Ring A is piperazin-1-yl the -NH- moiety may be optionally substituted by R^7; wherein

R^7 is selected from acetyl, methylsulphonyl, ethylsulphonyl and vinylsulphonyl; wherein R^7 may be optionally substituted on carbon by a group selected from R^{18}; wherein

R^{18} is selected from hydroxy, methoxy, acetoxy and dimethylamino.

Ring A is 4-methylsulphonylpiperazin-1-yl, 4-vinylsulphonylpiperazin-1-yl,4-acetylpiperazin-1-yl, 4-(acteoxyacetyl)piperazin-1-yl, 4-(hydroxyacetyl)piperazin-1-yl, 4-(dimethylaminoacetyl)piperazin-1-yl, 4-(2-dimethylaminoethylsulphonyl)piperazin-1-yl, 4-(2-methoxyethylsulphonyl)piperazin-1-yl, 4-(2-hydroxyethylsulphonyl)piperazin-1-yl, piperazin-1-yl or morpholino.

p is 0-2; wherein the values of R^1 may be the same or different.

p is 0 or 1.

p is 1.

p is 0.

q is 0 or 1.

q is 1.

q is 0.

R^3 is halo.

n is 0 or 1.

n is 1.

n is 0.

R^4 is C_{1-6}alkyl or carbocyclyl; wherein R^4 may be optionally substituted on carbon by one or more R^{12}; wherein

R^{12} is carbocyclyl.

R^4 is C_{1-4}alkyl or cyclobutyl; wherein R^4 may be optionally substituted on carbon by one or more R^{12}; wherein

R^{12} is cyclopropyl.

R^4 is ethyl, isopropyl, isobutyl, cyclobutyl or cyclopropylmethyl.

R^5 is C_{1-6}alkyl; wherein R^5 may be optionally substituted on carbon by one or more R^{14}; wherein

R^{14} is methoxy.

R^5 is C_{1-4}alkyl; wherein R^5 may be optionally substituted on carbon by one or more R^{14}; wherein

R^{14} is methoxy.

R^5 is methyl, ethyl, propyl or methoxymethyl.

R^6 is hydrogen.

Therefore in a further aspect of the invention there is provided a compound of formula (I) (as depicted above) wherein

Ring A is a nitrogen linked 6 membered saturated ring which optionally contains an additional nitrogen atom; wherein if Ring A contains an nitrogen atom that nitrogen may be optionally substituted by R^7; wherein

R^7 is selected from C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl and C_{2-6}alkenylsulphonyl; wherein R^7 may be optionally substituted on carbon by a group selected from R^{18}; wherein

R^{18} is selected from hydroxy, C_{1-6}alkoxy, C_{1-6}alkanoyloxy and *N,N*-(C_{1-6}alkyl)$_2$amino;

p is 0;

q is 0;

R^3 is halo;

n is 0 or 1.

R^4 is C_{1-6}alkyl or carbocyclyl; wherein R^4 may be optionally substituted on carbon by one or more R^{12}; wherein

R^{12} is carbocyclyl;

R^5 is C_{1-6}alkyl; wherein R^5 may be optionally substituted on carbon by one or more R^{14}; wherein

R^{14} is methoxy; and

R^6 is hydrogen.

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in a further aspect of the invention there is provided a compound of formula (I) (as depicted above) wherein

Ring A is 4-methylsulphonylpiperazin-1-yl, 4-vinylsulphonylpiperazin-1-yl,4-acetylpiperazin-1-yl, 4-(acteoxyacetyl)piperazin-1-yl, 4-(hydroxyacetyl)piperazin-1-yl, 4-(dimethylaminoacetyl)piperazin-1-yl, 4-(2-dimethylaminoethylsulphonyl)piperazin-1-yl, 4-(2-methoxyethylsulphonyl)piperazin-1-yl, 4-(2-hydroxyethylsulphonyl)piperazin-1-yl, piperazin-1-yl or morpholino;

p is 0;

q is 0;

R^3 is halo;

n is 0 or 1;

R^4 is ethyl, isopropyl, isobutyl, cyclobutyl or cyclopropylmethyl;

R^5 is methyl, ethyl, propyl or methoxymethyl; and

R^6 is hydrogen;

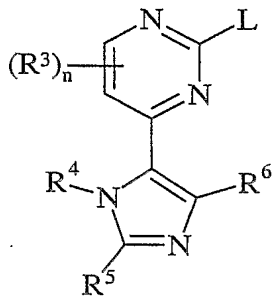
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

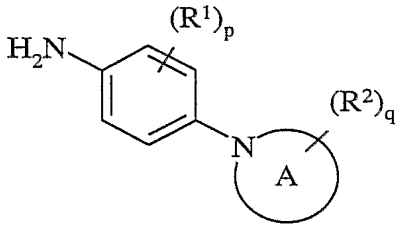
Another aspect of the present invention provides a process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula **(I)**) comprises of:

Process a) reaction of a pyrimidine of formula **(II)**:



(II)

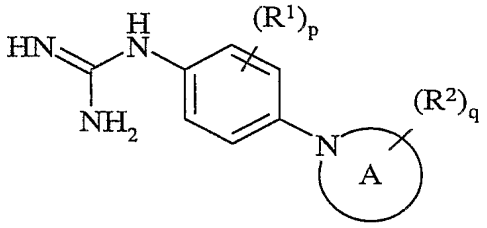
wherein L is a displaceable group; with an aniline of formula **(III)**:



(III)

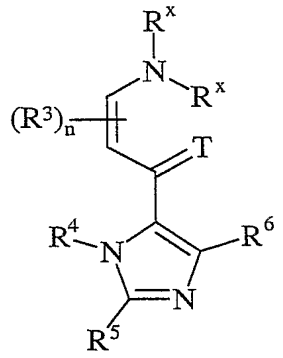
or

Process b) reacting a compound of formula **(IV)**:



(IV)

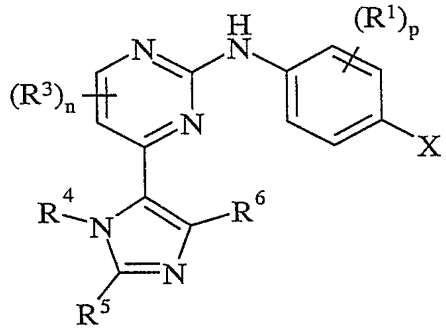
with a compound of formula **(V)**:



(V)

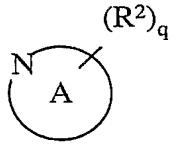
wherein T is O or S; R^x may be the same or different and is selected from C_{1-6}alkyl; or

Process c) reacting a pyrimidine of formula **(VI)**:



(VI)

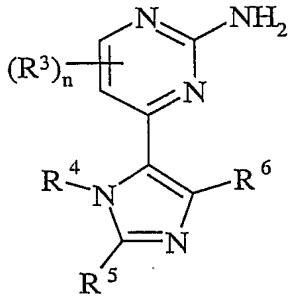
wherein X is a displaceable group; with a heterocyclyl of formula **(VII)**:



(VII)

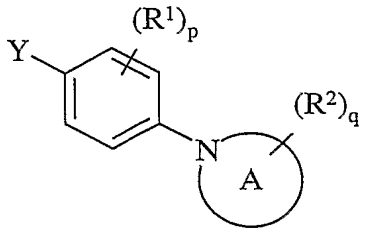
or

Process d) for compounds of formula **(I)**; reacting a pyrimidine of formula **(VIII)**



(VIII)

with a compound of formula **(IX)**:



(IX)

where Y is a displaceable group;

and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

X is a displaceable group, suitable values for X are for example, a bromo or iodo group. Preferably X is bromo.

Y is a displaceable group, suitable values for Y are for example, a halogeno or sulphonyloxy group, for example a bromo, iodo or trifluoromethanesulphonyloxy group. Preferably Y is iodo.

Specific reaction conditions for the above reactions are as follows.

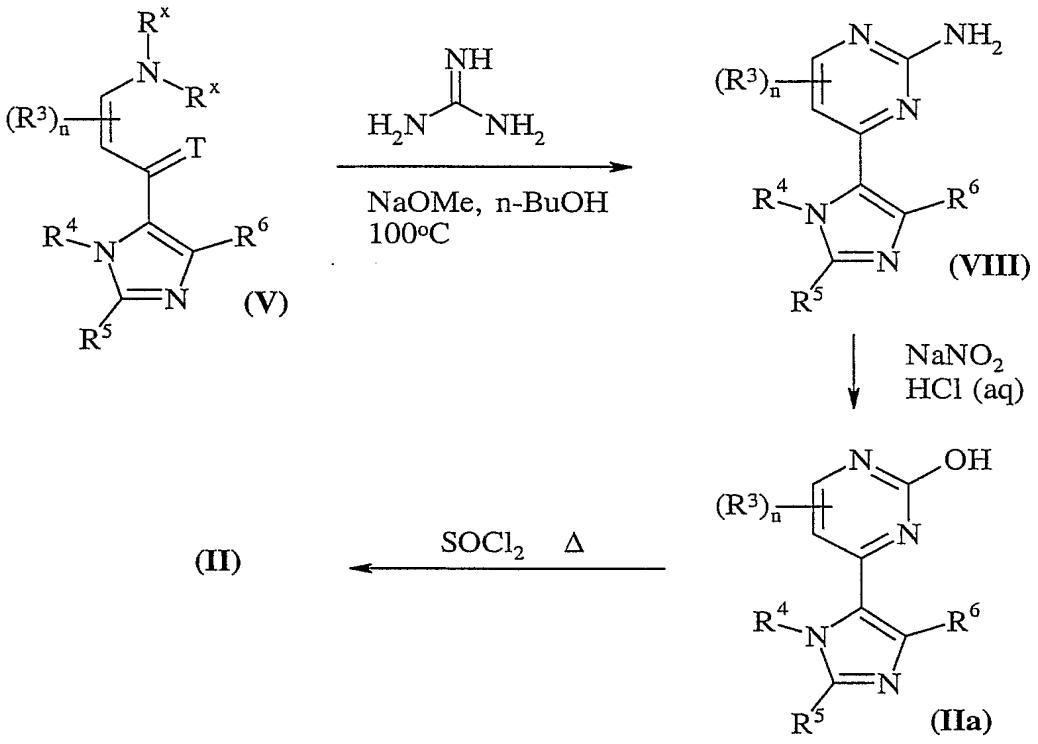
Process a) Pyrimidines of formula **(II)** and anilines of formula **(III)** may be reacted together:

i) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolidine, optionally in the presence of a suitable acid for example an inorganic acid such as hydrochloric acid or sulphuric acid, or an organic acid such as acetic acid or formic acid (or a suitable Lewis acid) and at a temperature in the range of 0°C to reflux, preferably reflux; or

ii) under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, **118**, 7215; *J. Am. Chem. Soc.*, **119**, 8451; *J. Org. Chem.*, **62**, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-*t*-butoxide, in the presence of a suitable ligand

such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range of 25 to 80°C.

Pyrimidines of the formula **(II)** where L is chloro may be prepared according to *Scheme 1*:

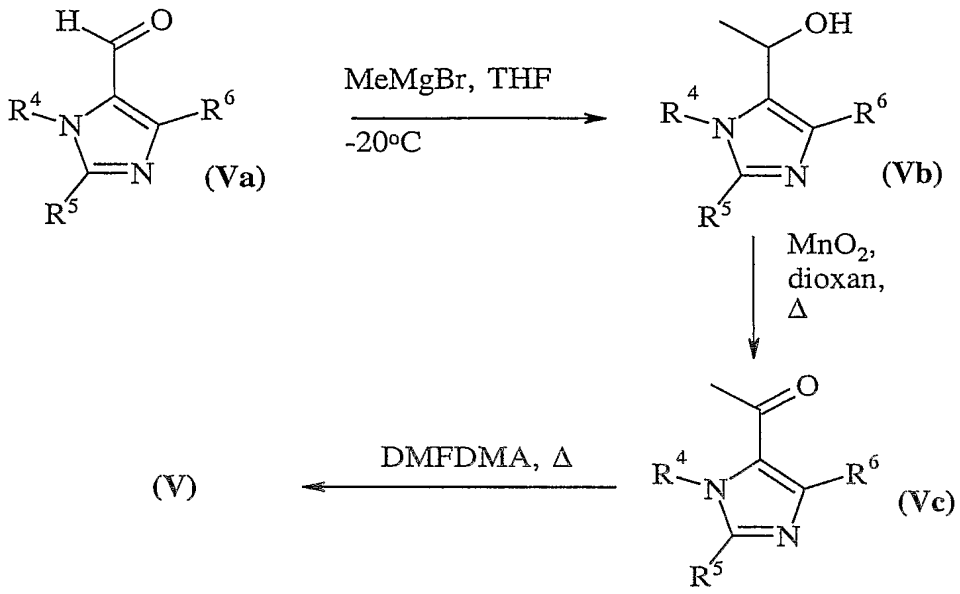


Scheme 1

Anilines of formula **(III)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process b) Compounds of formula **(IV)** and compounds of formula **(V)** are reacted together in a suitable solvent such as *N*-methylpyrrolidinone or butanol at a temperature in the range of 100-200°C, preferably in the range of 150-170°C. The reaction is preferably conducted in the presence of a suitable base such as, for example, sodium hydride, sodium methoxide or potassium carbonate.

Compounds of formula **(V)** may be prepared according to *Scheme 2*:



Scheme 2

Compounds of formula **(IV)** and **(Va)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process c) Compounds of formula **(VI)** and amines of formula **(VII)** may be reacted together under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, **118**, 7215; *J. Am. Chem. Soc.*, **119**, 8451; *J. Org. Chem.*, **62**, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-*t*-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range of 25 to 80°C.

Compounds of formula **(VI)** may be prepared according to the procedures described in WO 02/20512.

Heterocyclyls of formula **(VII)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process d) Compounds of formula **(VIII)** and amines of formula **(IX)** may be reacted together under standard Buchwald conditions as described in *Process a.*

The synthesis of compounds of formula **(VIII)** is described in *Scheme 1.*

Compounds of formula **(IX)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Amines of formula (**VI**) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such

as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possesses anti-cell-proliferation activity such as anti-cancer activity which is believed to arise from the CDK inhibitory activity of the compound. These properties may be assessed, for example, using the procedure set out below:-

Assay

The following abbreviations have been used :-

HEPES is *N*-[2-Hydroxyethyl]piperazine-*N*'-[2-ethanesulfonic acid]

DTT is Dithiothreitol

PMSF is Phenylmethylsulphonyl fluoride

The compounds were tested in an *in vitro* kinase assay in 96 well format using Scintillation Proximity Assay (SPA - obtained from Amersham) for measuring incorporation of [γ-33-P]-Adenosine Triphosphate into a test substrate (GST-Retinoblastoma protein; GST-Rb). In each well was placed the compound to be tested (diluted in DMSO and water to correct concentrations) and in control wells either roscovitine as an inhibitor control or DMSO as a positive control.

Approximately 0.2μl of CDK2/Cyclin E partially-purified enzyme (amount dependent on enzyme activity) diluted in 25μl incubation buffer was added to each well then 20μl of GST-Rb/ATP/ATP33 mixture (containing 0.5μg GST-Rb and 0.2μM ATP and 0.14μCi [γ-33-P]-Adenosine Triphosphate in incubation buffer), and the resulting mixture shaken gently, then incubated at room temperature for 60 minutes.

To each well was then added 150μL stop solution containing (0.8mg/well of Protein A-PVT SPA bead (Amersham)), 20pM/well of Anti-Glutathione Transferase, Rabbit IgG (obtained from Molecular Probes), 61mM EDTA and 50mM HEPES pH 7.5 containing 0.05% sodium azide.

The plates were sealed with Topseal-S plate sealers, left for two hours then spun at 2500rpm, 1124xg., for 5 minutes. The plates were read on a Topcount for 30 seconds per well.

The incubation buffer used to dilute the enzyme and substrate mixes contained 50mM HEPES pH7.5, 10mM $MnCl_2$, 1mM DTT, 100μM Sodium vanadate, 100μM NaF, 10mM Sodium Glycerophosphate, BSA (1mg/ml final).

Test substrate

In this assay only part of the retinoblastoma protein (Science 1987 Mar13;235(4794):1394-1399; Lee W.H., Bookstein R., Hong F., Young L.J., Shew J.Y., Lee E.Y.) was used, fused to a GST tag. PCR of retinoblastoma gene encoding amino acids 379-928 (obtained from retinoblastoma plasmid ATCC pLRbRNL) was performed, and the sequence cloned into pGEx 2T fusion vector (Smith D.B. and Johnson, K.S. Gene 67, 31 (1988); which contained a tac promoter for inducible expression, internal lac I^q gene for use in any E.Coli host, and a coding region for thrombin cleavage - obtained from Pharmacia Biotech) which was used to amplify amino acids 792-928. This sequence was again cloned into pGEx 2T.

The retinoblastoma 792-928 sequence so obtained was expressed in E.Coli (BL21 (DE3) pLysS cells) using standard inducible expression techniques, and purified as follows.

E.coli paste was resuspended in 10ml/g of NETN buffer (50mM Tris pH 7.5, 120mM NaCl, 1mM EDTA, 0.5%v/v NP-40, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) and sonicated for 2 x 45 seconds per 100ml homogenate. After centrifugation, the supernatant was loaded onto a 10ml glutathione Sepharose column (Pharmacia Biotech, Herts, UK), and washed with NETN buffer. After washing with kinase buffer (50mM HEPES pH 7.5, 10mM MgCl2, 1mM DTT, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) the protein was eluted with 50mM reduced glutathione in kinase buffer. Fractions containing GST-Rb(792-927) were pooled and dialysed overnight against kinase buffer. The final product was analysed by Sodium Dodeca Sulfate (SDS) PAGE (Polyacrylamide gel) using 8-16% Tris-Glycine gels (Novex, San Diego, USA).

CDK2 and Cyclin E

The open reading frames of CDK2 and Cyclin E were isolated by reverse transcriptase-PCR using HeLa cell and activated T cell mRNA as a template and cloned into the insect expression vector pVL1393 (obtained from Invitrogen 1995 catalogue number: V1392-20). CDK2 and cyclin E were then dually expressed [using a standard virus Baculogold co-infection technique] in the insect SF21 cell system (Spodoptera Frugiperda cells derived from ovarian tissue of the Fall Army Worm - commercially available).

Example production of Cyclin E/CDK2

The following Example provides details of the production of Cyclin E/CDK2 in SF21 cells (in TC100 + 10% FBS(TCS) + 0.2% Pluronic) having dual infection MOI 3 for each virus of Cyclin E & CDK2.

SF21 cells grown in a roller bottle culture to 2.33 x 10^6 cells/ml were used to inoculate 10 x 500 ml roller bottles at 0.2 x 10E6 cells/ml. The roller bottles were incubated on a roller rig at 28°C.

After 3 days (72 hrs.) the cells were counted, and the average from 2 bottles found to be 1.86 x 10E6 cells/ml. (99% viable). The cultures were then infected with the dual viruses at an MOI 3 for each virus.

The viruses were mixed together before addition to the cultures, and the cultures returned to the roller rig 28°C.

After 2 days (48 hrs.) post infection the 5 Litres of culture was harvested. The total cell count at harvest was 1.58 x 10E6 cells/ml.(99% viable). The cells were spun out at 2500rpm, 30 mins., 4°C in Heraeus Omnifuge 2.0 RS in 250 ml. lots. The supernatant was discarded.

Partial co-purification of Cdk2 and Cyclin E

Sf21 cells were resuspended in lysis buffer (50mM Tris pH 8.2, 10mM $MgCl_2$, 1mM DTT, 10mM glycerophosphate, 0.1mM sodium orthovanadate, 0.1mM NaF, 1mM PMSF, 1ug/ml leupeptin and 1ug/ml aprotinin) and homogenised for 2 minutes in a 10ml Dounce homgeniser. After centrifugation, the supernatant was loaded onto a Poros HQ/M 1.4/100 anion exchange column (PE Biosystems, Hertford, UK). Cdk2 and Cyclin E were coeluted at the beginning of a 0-1M NaCl gradient (run in lysis buffer minus protease inhibitors) over 20 column volumes. Co-elution was checked by western blot using both anti-Cdk2 and anti-Cyclin E antibodies (Santa Cruz Biotechnology, California, US).

By analogy, assays designed to assess inhibition of CDK1 and CDK4 may be constructed. CDK2 (EMBL Accession No. X62071) may be used together with Cyclin A or Cyclin E (see EMBL Accession No. M73812), and further details for such assays are contained in PCT International Publication No. WO99/21845, the relevant Biochemical & Biological Evaluation sections of which are hereby incorporated by reference.

Although the pharmacological properties of the compounds of the formula **(I)** vary with structural change, in general activity possessed by compounds of the formula **(I)** may be demonstrated at IC_{50} concentrations or doses in the range 250μM to 1nM.

When tested in the above in-vitro assay the CDK2 inhibitory activity of Example 8 was measured as $IC_{50} = 0.181\mu M$.

The *in vivo* activity of the compounds of the present invention may be assessed by standard techniques, for example by measuring inhibition of cell growth and assessing cytotoxicity.

Inhibition of cell growth may be measured by staining cells with Sulforhodamine B (SRB), a fluorescent dye that stains proteins and therefore gives an estimation of amount of protein (i.e. cells) in a well (see Boyd, M.R.(1989) Status of the NCI preclinical antitumour drug discovery screen. Prin. Prac Oncol 10:1-12). Thus, the following details are provided of measuring inhibition of cell growth:-

Cells were plated in appropriate medium in a volume of 100μl in 96 well plates; media was Dulbecco's Modified Eagle media for MCF-7, SK-UT-1B and SK-UT-1. The cells were allowed to attach overnight, then inhibitor compounds were added at various concentrations in a maximum concentration of 1% DMSO (v/v). A control plate was assayed to give a value for cells before dosing. Cells were incubated at 37°C, (5% CO_2) for three days.

At the end of three days TCA was added to the plates to a final concentration of 16% (v/v). Plates were then incubated at 4°C for 1 hour, the supernatant removed and the plates washed in tap water. After drying, 100µl SRB dye (0.4% SRB in 1% acetic acid) was added for 30 minutes at 37°C. Excess SRB was removed and the plates washed in 1% acetic acid. The SRB bound to protein was solubilised in 10mM Tris pH7.5 and shaken for 30 minutes at room temperature. The ODs were read at 540nm, and the concentration of inhibitor causing 50% inhibition of growth was determined from a semi-log plot of inhibitor concentration versus absorbance. The concentration of compound that reduced the optical density to below that obtained when the cells were plated at the start of the experiment gave the value for toxicity.

Typical IC_{50} values for compounds of the invention when tested in the SRB assay are in the range 1mM to 1nM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a pyrimidine derivative of the formula (**I**), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (**I**) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (**I**), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as

defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are effective cell cycle inhibitors (anti-cell proliferation agents), which property is believed to arise from their CDK inhibitory properties. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by CDK enzymes, i.e. the compounds may be used to produce a CDK inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation of malignant cells characterised by inhibition of CDK enzymes, i.e. the compounds may be used to produce an anti-proliferative effect mediated alone or in part by the inhibition of CDKs. Such a compound of the invention is expected to possess a wide range of anti-cancer properties as CDKs have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a compound of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a compound of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with CDKs, especially those tumours which are significantly dependent on CDKs for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

It is further expected that a compound of the present invention will possess activity against other cell-proliferation diseases in a wide range of other disease states including leukaemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Thus according to this aspect of the invention there is provided a compound of the formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as

defined hereinbefore for use as a medicament; and the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man. Particularly, an inhibitory effect is produced by preventing entry into, or progression through, the S phase by inhibition of CDK2 and CDK4, especially CDK2, and M phase by inhibition of CDK1.

According to a further feature of the invention, there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in the manufacture of a medicament for use in the treatment of cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, particularly in the treatment of cancers.

According to a further feature of this aspect of the invention there is provided a method for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound as defined immediately above. Particularly, an inhibitory effect is produced by preventing entry into, or progression through, the S phase by inhibition of CDK2 and CDK4, especially CDK2, and M phase by inhibition of CDK1.

According to a further feature of this aspect of the invention there is provided a method for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof as defined herein before. Particularly, an inhibitory effect is produced by preventing entry into, or progression through, the S phase by inhibition of CDK2 and CDK4, especially CDK2, and M phase by inhibition of CDK1.

According to an additional feature of this aspect of the invention there is provided a method of treating cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm-blooded animal, such as man, in need of such treatment which

comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof as defined herein before.

Particularly there is provided a method of treating cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as defined herein before.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancer in a warm-blooded animal such as man.

Preventing cells from entering DNA synthesis by inhibition of essential S-phase initiating activities such as CDK2 initiation may also be useful in protecting normal cells of the body from toxicity of cycle-specific pharmaceutical agents. Inhibition of CDK2 or 4 will prevent progression into the cell cycle in normal cells which could limit the toxicity of cycle-specific pharmaceutical agents which act in S-phase, G2 or mitosis. Such protection may result in the prevention of hair loss normally associated with these agents.

Therefore in a further aspect of the invention there is provided a compound of formula

(I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use as a cell protective agent.

Therefore in a further aspect of the invention there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use in preventing hair loss arising from the treatment of malignant conditions with pharmaceutical agents.

Examples of pharmaceutical agents for treating malignant conditions that are known to cause hair loss include alkylating agents such as ifosfamide and cyclophosphamide; antimetabolites such as methotrexate, 5-fluorouracil, gemcitabine and cytarabine; vinca alkaloids and analogues such as vincristine, vinbalstine, vindesine, vinorelbine; taxanes such as paclitaxel and docetaxel; topoisomerase I inhibitors such as irintotecan and topotecan; cytotoxic antibiotics such as doxorubicin, daunorubicin, mitoxantrone, actinomycin-D and mitomycin; and others such as etoposide and tretinoin.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, may be administered in association with a one or more of the above pharmaceutical agents. In this instance the compound of formula (I) may be administered by systemic or non systemic means. Particularly the compound of formula (I) my may administered by non-systemic means, for example topical administration.

Therefore in an additional feature of the invention, there is provided a method of preventing hair loss during treatment for one or more malignant conditions with pharmaceutical agents, in a warm-blooded animal, such as man, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In an additional feature of the invention, there is provided a method of preventing hair loss during treatment for one or more malignant conditions with pharmaceutical agents, in a warm-blooded animal, such as man, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof in simultaneous, sequential or separate administration with an effective amount of said pharmaceutical agent.

According to a further aspect of the invention there is provided a pharmaceutical composition for use in preventing hair loss arising from the treatment of malignant conditions with pharmaceutical agents which comprises a compound of formula (I), or a

pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and said pharmaceutical agent, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and a pharmaceutical agent for treating malignant conditions that is known to cause hair loss.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in a first unit dosage form;

b) a pharmaceutical agent for treating malignant conditions that is known to cause hair loss; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in the manufacture of a medicament for the prevention of hair loss during treatment of malignant conditions with pharmaceutical agents.

According to a further aspect of the present invention there is provided a combination treatment for the prevention of hair loss comprising the administration of an effective amount of a compound of the formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a pharmaceutical agent for treatment of malignant conditions to a warm-blooded animal, such as man.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

The CDK inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of

medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the cell cycle inhibitory treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other cell cycle inhibitory agents that work by the same or different mechanisms from those defined hereinbefore;

(ii) cytostatic agents such as antioestrogens (for example tamoxifen,toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan). According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula **(I)** as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer.

In addition to their use in therapeutic medicine, the compounds of formula **(I)** and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following non limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-d_6) as solvent unless otherwise indicated;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) solvent ratios are given in volume:volume (v/v) terms; and

(x) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z

are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is $(MH)^+$;

(xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulphur atom have not been resolved;

(xii) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;

(xvi) the following abbreviations have been used:

THF	tetrahydrofuran;
DMF	*N,N*-dimethylformamide;
DMFDMA	dimethylformamide dimethylacetal;
EtOAc	ethyl acetate;
MeOH	methanol;
EtOH	ethanol;
DCM	dichloromethane; and
DMSO	dimethylsulphoxide.

xvii) where an Isolute SCX-2 column is referred to, this means an "ion exchange" extraction cartridge for adsorption of basic compounds, i.e. a polypropylene tube containing a benzenesulphonic acid based strong cation exchange sorbent, used according to the manufacturers instructions obtained from International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ;

xviii) where an Isolute amine column is referred to, this means an "ion exchange" extraction cartridge for adsorption of acidic compounds, i.e. a polypropylene tube containing a amino silane covalently bonded to a silica particle used according to the manufacturers instructions obtained from International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ;

xix) where a Chemelut column is referred to, this means an extraction cartridge for removal of water, i.e. a polypropylene tube containing diatomaceous earth used according to the manufacturers instructions obtained from Varian, Harbor City, California, USA.

Example 1

2-[4-(4-Mesylpiperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

2-Amino-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Method 39 of WO 03/076436; 220mg, 1mmol), 1-bromo-4-(4-mesylpiperazinyl)benzene (WO 2001062742; 319mg, 1mmol), tris(dibenzylideneacetone)dipalladium(0) (23mg, 2mol%), 2-(di-tert-butylphosphino)biphenyl (6mg, 2 mol%) and sodium tert-butoxide (135 mg, 1.4 mmol) in anhydrous 1,4-dioxane (10ml) was evacuated and refilled with nitrogen (3 times). The reaction was heated under nitrogen at 95°C overnight before evaporating under reduced pressure. The residue was triturated with ethyl acetate (20ml), filtered and re-evaporated to give a gum. Chromatography on silica gel with methanol:DCM (2:98 to 5:95) gave the title compound as a yellow solid. (70 mg 15%). NMR: 1.39 (d, 6H), 2.47 (s, 3H), 2.92 (s, 3H), 3.17 (m, 4H), 3.26 (m, 4H), 5.70 (septuplet, 1H), 6.92 (d, 2H), 6.94 (d, 1H), 7.39 (s, 1H), 7.48 (d, 2H), 8.32 (d, 1H), 9.18 (s, 1H); m/z 456.

Example 2

2-[4-(4-Mesylpiperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-chloropyrimidine

The title compound was prepared according to the procedure of Example 1 using 2-amino-5-chloro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Method 5) heating for 30 hours at 100°C. Chromatography on silica gel with methanol:DCM (2:98 to 6:94). NMR 1.36 (d, 6H), 2.46 (s, 3H), 2.80 (s, 3H), 3.16 (m, 4H), 3.23 (m, 4H), 4.79 (septuplet, 1H), 6.91 (d, 2H), 7.22 (s, 1H), 7.49 (d, 2H), 8.51 (d, 1H), 9.49 (s, 1H); m/z 490.

Example 3

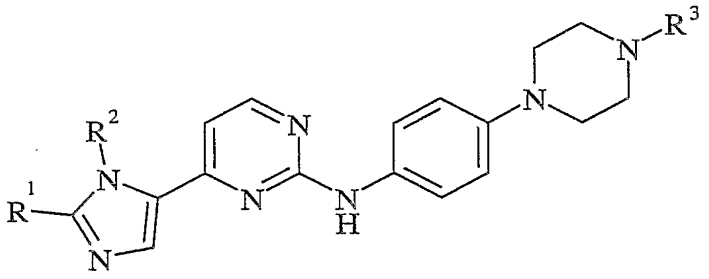
2-[4-(4-Mesylpiperazin-1-yl)anilino]-4-(1-cyclobutyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

5-(3-Dimethylaminoprop-2-en-1-oyl)-1-cyclobutyl-2-methylimidazole (Method 37 of WO 03/076435; 233 mg 1 mmol) and N-{4-[4-(methylsulphonyl)piperazin-1-yl]phenyl} guanidine (Method 1; 390 mg 1.3mmol) in 2-methoxyethanol (8 ml) was stirred and heated for 18 hours at 110°C. The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with methanol:DCM (3:97 to 8:92). After evaporation and trituration with ether, the title compound was obtained as a yellow solid. (227 mg 48.5%). NMR: 1.60 - 1.71 (2xm, 2H), 2.36 (m, 4H), 2.49 (s, 3H), 2.91 (s, 3H), 3.18 (m,

4H), 3.25 (m, 4H), 5.51 (quintet, 1H), 6.91 (d, 1H), 6.97 (d, 2H), 7.30 (s, 1H), 7.54 (d, 2H), 8.33 (d, 1H), 9.23 (s, 1H); m/z 468.

Examples 4-17

The following compounds were prepared by the procedure of Example 3 using the appropriate imidazole and N-{4-[4-(methylsulphonyl)piperazin-1-yl]phenyl}guanidine (Method 1) or *N*-[4-(4-acetylpiperazin-1-yl)phenyl]guanidine (Method 2).



Ex	R^1	R^2	R^3	NMR	m/z	SM
4 [1]	Me	Cyclopropyl-methyl	$MeSO_2$-	0.09 (m, 2H), 0.28 (m, 2H), 1.00 (m, 1H), 2.39 (s, 3H), 2.92 (s, 3H), 3.18 (m, 4H), 3.24 (m, 4H), 4.49 (d, 2H), 6.94 (d, 2H), 7.02 (d, 1H), 7.47 (d, 2H), 7.58 (s, 1H), 8.30 (d, 1H), 9.15 (s, 1H)	468	Meth 41 in WO 03/076435
5 [2]	Et	Et	$MeSO_2$-	1.11 (t, 3H), 1.24 (t, 3H), 2.71 (q, 2H), 2.91 (s, 3H), 3.18 (m, 4H), 3.23 (m, 4H), 4.50 (q, 2H), 6.95 (d, 2H), 7.03 (d, 1H), 7.47 (d, 2H), 7.61 (s, 1H), 8.28 (d, 1H), 9.12 (s, 1H)	456	Meth 55 of WO 03/076434

Ex	R^1	R^2	R^3	NMR	m/z	SM
6 [3]	Et	*i*-Pr	$MeSO_2$-	1.28 (t, 3H), 1.40 (d, 6H), 2.79 (q, 2H), 2.91 (s, 3H), 3.17 (m, 4H), 3.24 (m, 4H), 5.61 (septuplet, 1H), 6.93 (d, 2H), 6.94 (d, 1H), 7.40 (s, 1H), 7.49 (d, 2H), 8.32 (d, 1H), 9.18 (s, 1H)	470	Meth 9
7 [4]	$MeOCH_2$-	*i*-Pr	$MeSO_2$-	1.42 (d, 6H), 2.92 (s, 3H), 3.17 (m, 4H), 3.24 (m, 4H),3.27 (s, 3H),4.53 (s, 2H), 5.52 (septuplet, 1H), 6.94 (d, 2H), 6.99 (d, 1H), 7.47 (s, 1H), 7.49 (d, 2H), 8.38 (d, 1H), 9.21 (s, 1H)	486	Meth 50 of WO 03/076434
8 [5]	Pr	Et	$MeSO_2$-	0.97 (t, 3H), 1.12 (t, 3H), 1.72 (sextuplet, 2H), 2.68 (t, 2H), 2.92 (s, 3H), 3.16 (m, 4H), 3.27 (m, 4H), 4.51 (q, 2H), 6.93 (d, 2H), 7.02 (d, 1H), 7.48 (d, 2H), 7.62 (s, 1H), 8.29 (d, 1H), 9.12 (s, 1H)	470	Meth 13
9 [6]	Me	Et	$MeSO_2$-	1.12 (t, 3H), 2.38 (s, 3H), 2.91 (s, 3H), 3.17 (m, 4H), 3.24 (m, 4H), 4.50 (q, 2H), 6.94 (d, 2H), 7.02 (d, 1H), 7.48 (d, 2H), 7.60 (s, 1H), 8.29 (d, 1H), 9.13 (s, 1H)	442	Meth 16 of WO 02/20512

Ex	R^1	R^2	R^3	NMR	m/z	SM
107	Me	*i*-Bu	$MeSO_2$-	0.60 (d, 6H), 1.69 (septuplet, 1H), 2.36 (s, 3H), 2.92 (s, 3H), 3.16 (m, 4H), 3.25 (m, 4H), 4.32 (d, 2H), 6.94 (d, 2H), 7.01 (d, 1H), 7.47 (d, 2H), 7.58 (s, 1H), 8.29 (d, 1H), 9.18 (s, 1H)	470	Meth 29 of WO 03/076436
118	Et	*i*-Pr	MeC(O)-	1.28 (t, 3H), 1.40 (d, 6H), 2.02 (s, 3H), 2.79 (q, 2H), 3.00 (t, 2H), 3.08 (t, 2H), 3.57 (m, 4H), 5.60 (septuplet, 1H), 6.91 (d, 2H), 6.94 (d, 1H), 7.41 (s, 1H), 7.48 (d, 2H), 8.31 (d, 1H), 9.18 (s, 1H)	434	Meth 9
12	Pr	Et	MeC(O)-	0.95 (t, 3H), 1.10 (t, 3H), 1.70 (septuplet, 2H), 2.02 (s, 3H), 2.68 (t, 2H), 3.01 (t, 2H), 3.08 (t, 2H), 3.59 (q, 4H), 4.51 (q, 2H), 6.92 (d, 2H), 7.02 (d, 1H), 7.44 (d, 2H), 7.62 (s, 1H), 8.29 (d, 1H), 9.11 (s, 1H)	434	Meth 13

Ex	R^1	R^2	R^3	NMR	m/z	SM
13	Me	Cyclobutyl	MeC(O)-	1.60 (sextet, 1H), 1.73 (q, 1H), 2.05 (s, 3H), 2.30-2.48 (m, 4H), 3.031 (t, 2H), 3.09 (t, 2H), 3.59 (q, 4H), 5.58 (quintet, 1H), 6.93 (d, 1H), 6.96 (d, 2H), 7.32 (s, 1H), 7.57 (d, 2H), 8.34 (d, 1H), 9.24 (s, 1H)	432	Meth 37 of WO 03/076435
14	Et	Et	MeC(O)-	1.12 (t, 3H), 1.24 (t, 3H), 2.03 (s, 3H), 2.71 (q, 2H), 3.01 (t, 2H), 3.08 (t, 2H), 3.57 (q, 4H), 4.49 (q, 2H), 6.92 (d, 2H), 7.01 (d, 1H), 7.45 (d, 2H), 7.61 (s, 1H), 8.29 (d, 1H), 9.10 (s, 1H)	420	Meth 55 of WO 03/076434
15	Me	Et	MeC(O)-	1.11 (t, 3H), 2.03 (s, 3H), 2.38 (s, 3H), 3.02 (t, 2H), 3.08 (t, 2H), 3.57 (q, 4H), 4.50 (q, 2H), 6.92 (d, 2H), 7.01 (d, 1H), 7.46 (d, 2H), 7.59 (s, 1H), 8.28 (d, 1H), 9.09 (s, 1H)	406	Meth 16 of WO 02/20512
169	$MeOCH_2$-	*i*-Pr	MeC(O)-	1.42 (d, 6H), 2.03 (s, 3H), 3.01 (t, 2H), 3.08 (t, 2H), 3.27 (s, 3H), 3.57 (q, 4H), 4.53 (s, 2H), 5.52 (septuplet, 1H), 6.91 (d, 2H), 6.99 (d, 1H), 7.44 (s, 1H), 7.47 (d, 2H), 8.38 (d, 1H), 9.20 (s, 1H)	450	Meth 50 of WO 03/076434

Ex	R^1	R^2	R^3	NMR	m/z	SM
17 [10]	Me	*i*-Bu	MeC(O)-	0.60 (d, 6H), 1.69 (septuplet, 1H), 2.02 (s, 3H), 2.35 (s, 3H), 2.99 (t, 2H), 3.07 (t, 2H), 3.58 (q, 4H), 4.33 (d, 2H), 6.93 (d, 2H), 7.00 (d, 1H), 7.45 (d, 2H), 7.58 (s, 1H), 8.28 (d, 1H), 9.13 (s, 1H)	434	Meth 29 of WO 03/076436

[1] This compound required further chromatography on neutral alumina (activity II) eluting with EtOAc:DCM (1:1) then EtOAc:DCM (1:1) with 5%v/v methanol. The title compound was crystallised from methanol. (120 mg 25.6%).

[2] Chromatography with methanol:DCM (2:98 to 6:94). The title compound was crystallised from acetonitrile. (149 mg 32.7%)

[3] Chromatography with methanol:DCM (3:97 to 5:95). (127 mg 27%).

[4] Chromatography with methanol:DCM (3:97). (180 mg 37%).

[5] Chromatography with methanol:DCM (2:98 to 6:94). (290 mg 34.5%).

[6] Chromatography with methanol:DCM (2:98 to 6:94). (340 mg 38.5%).

[7] Chromatography with methanol:DCM (2:98 to 6:94). (350 mg 41.7%).

[8] (2*E*)-3-(Dimethylamino)-1-(2-ethyl-1-isopropyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Meth 9; 470 mg 2 mmol) and 4-(4-acetylpiperazin-1-yl)phenylguanidine bicarbonate (Method 2; 740 mg 2.3mmol) in 2-methoxyethanol (10 ml) was stirred and heated for 24 hours at 110°C. The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with methanol:DCM (2:98 to 6:94). After evaporation and trituration with ether, the title compound was obtained as a yellow solid. (290 mg 33.4%).

[9] Chromatography with methanol:DCM (3:97 to 8:92). (186 mg 20.7%).

[10] Chromatography with methanol:DCM (2:98 to 6:94). (372 mg 40%).

Example 18

2-[4-(4-Acetylpiperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

(2*E*)-3-(Dimethylamino)-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 24 of WO 03/076436; 140 mg 0.63 mmol) and 4-(4-acetylpiperazin-1-yl)phenyl

guanidine bicarbonate (Method 2; 240 mg 0.74 mmol) in 2-methoxyethanol (4 ml) were reacted under nitrogen under microwave conditions at 200°C for 30 minutes. After evaporation under reduced pressure, chromatography on silica gel with methanol:DCM (2:98 to 6:94) gave the title compound , after ether trituration, as a yellow solid. (85 mg 31.5%). NMR: 1.39 (d, 6H), 2.02 (s, 3H), 2.45 (s, 3H), 3.00 (b t, 2H), 3.06 (b t, 2H), 3.56 (b q, 4H), 5.70 (septuplet, 1H), 6.91 (d, 2H), 6.95 (d, 1H), 7.38 (s, 1H), 7.46 (d, 2H), 8.31 (d, 1H), 9.15 (s, 1H); m/z 420.

Example 19

2-[4-(4-Acetylpiperazin-1-yl)anilino]-4-[1-(cyclopropylmethyl)-2-methyl-1*H*-imidazol-5-yl]pyrimidine

The title compound was prepared by the procedure of Example 18 except that the reaction was heated in microwave at 200°C for 40 minutes. 148 mg 53.4%. NMR: 0.10 (m, 2H), 0.28 (m, 2H), 1.02 (m, 1H), 2.03 (s, 3H), 2.38 (s, 3H), 3.01 (t, 2H), 3.08 (t, 2H), 3.57 (q, 4H), 4.48 (d, 2H), 6.92 (d, 2H), 7.01 (d, 1H), 7.43 (d, 2H), 7.57 (s, 1H), 8.281 (d, 1H), 9.12 (s, 1H); m/z 432.

Example 20

2-[4-(Piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

2-[4-(4-Acetylpiperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Example 18; 1.3g) was stirred and heated in isopropanol (15ml) and 33% hydrochloric acid (1.5ml) at 90°C for 4.5 hours. The reaction was evaporated under reduced pressure and then basified with 7N ammonia in methanol and re-evaporated. Toluene was added and the mixture was re-evaporated (3 times). The residue was purified by chromatography on neutral alumina, activity II eluting with methanol:DCM (5:95) to give the title compound as a yellow gum. (330 mg 28%). NMR: 1.40 (d, 6H), 2.46 (s, 3H), 2.82 (m, 4H), 2.96 (m, 4H), 5.69 (septuplet, 1H), 6.85 (d, 2H), 6.93 (d, 1H), 7.18 (s, 1H), 7.42 (d, 2H), 8.30 (d, 1H), 9.11 (s, 1H); m/z 378.

Example 21

2-{4-[4-(2-Acetoxyacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

2-[4-(Piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Example 20; 330mg 0.88 mmol) was stirred in DCM (6ml) at room temperature. Triethylamine was added (153mg 1.51 mmol) followed by dropwise addition of acetoxyacetylchloride (143 mg 1.05 mmol). After stirring for 1.25 hours, DCM (10 ml) and brine (5 ml) were added. The reaction was stirred vigorously for 10 minutes then the organic layers were separated, dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound as a yellow foam. Quantitative yield. The solid was triturated with ether and re-evaporated. NMR: 1.40 (d, 6H), 2.08 (s, 3H), 2.48 (s, 3H), 3.05 (b d, 4H), 3.54 (b d, 4H), 4.81 (s, 2H), 5.70 (septuplet, 1H), 6.92 (d, 2H), 6.95 (d, 1H), 7.40 (s, 1H), 7.48 (d, 2H), 8.31 (d, 1H), 9.18 (s, 1H); m/z 478.

Example 22

2-{4-[4-(2-Hydroxyacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

2-{4-[4-(2-Acetoxyacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Example 21; 330mg) was stirred in methanol (5 ml) at room temperature and 7N ammonia in methanol (1.6 ml) was added. After 28 hours, the reaction was evaporated under reduced pressure. Chromatography on silica gel using methanol:DCM (4:96 to 5:95), yielded the title compound as a yellow solid. (108 mg 36%). NMR: 1.39 (d, 6H), 2.46 (s, 3H), 3.05 (b s, 4H), 3.48 (b s, 2H), 3.61 (b s, 2H), 4.12 (d, 2H), 4.57 (t, 1H), 5.69 (septuplet, 1H), 6.92 (d, 2H), 6.95 (d, 1H), 7.38 (s, 1H), 7.47 (d, 2H), 8.31 (d, 1H), 9.15 (s, 1H); m/z 436.

Example 23

2-{4-[4-(2-Dimethylaminoacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

Chloroacetyl chloride (50μl, 0.65 mmol) was added dropwise to a stirred solution of 2-[4-(piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Example 20; 200 mg, 0.53 mmol) and triethylamine (90 μl, 0.65 mmol) in DCM (5 ml) at room temperature. After 50 minutes, 2M dimethylamine in THF solution (2 ml, 4mmol) was added

and the reaction was stirred for 5 hours before evaporating under reduced pressure. Chromatography on neutral alumina (activity II) with methanol:DCM (1:99 to 3:97) gave material which required further purification on silica gel with methanol:DCM:7N NH_3 MeOH (3:97:.0025 to 10:90:.0025) to give the title compound as a yellow foam. (150 mg 60% yield). NMR: 1.39 (d, 6H), 2.19 (s, 6H), 2.46 (s, 3H), 3.02 (b t, 2H), 3.06 (b t, 2H), 3.59 (b t, 2H), 3.68 (b t, 2H), 5.69 (septuplet, 1H), 6.92 (d, 2H), 6.94 (d, 1H), 7.39 (s, 1H), 7.47 (d, 2H), 8.31 (d, 1H), 9.17 (s, 1H); m/z 463.

Example 24

2-{4-[4-(Vinylsulphonyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

2-[4-(Piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Example 20; 370mg 0.98 mmol) was stirred in DCM (10 ml) at room temperature. Triethylamine (150mg 1.49 mmol) was added followed by dropwise addition of 2-chloro-1-ethanesulphonyl chloride (196 mg 1.2 mmol) in DCM (1 ml). After stirring for 1.25 hours, the reaction was evaporated under reduced pressure and triturated with ether. The resulting solid was treated with water (15 ml), the basified with saturated sodium hydrogen carbonate solution and extracted into DCM (2x20 ml). The organics were washed with brine (10 ml), dried ($MgSO_4$) and evaporated to give a gum. After chromatography on silica gel using methanol:DCM (3:97 to 5:95), the title compound was obtained as a yellow solid (140 mg 30.4%). NMR 1.39 (d, 6H), 2.46 (s, 3H), 3.16 (s, 8H), 5.68 (septuplet, 1H), 6.20 (d, 1H), 6.85 (dd, 1H), 6.91 (d, 2H), 6.95 (d, 1H), 7.38 (s, 1H), 7.47 (d, 2H), 8.30 (d, 1H), 9.16 (s, 1H); m/z 468.

Example 25

2-{4-[4-(2-Dimethylaminoethylsulphonyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

Dimethylamine (2.0M) in THF (1.5 ml) was added to a stirred suspension of 2-{4-[4-(vinylsulphonyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl) pyrimidine (Example 24; 140 mg 0.3 mmol) in THF (3 ml) at room temperature. Additional dimethylamine solution (0.5 ml) was added after 2 hours. The reaction was stirred for 1 hour then stood overnight. The reaction was evaporated under reduced pressure, triturated with ether and filtered to give the title compound as a yellow solid. (134mg 89%). NMR: 1.40 (d,

6H), 2.46 (s, 3H), 2.62 (t, 2H), 3.13 (t, 4H), 3.20-3.35 (2H and 4H)[under exchangeables], 5.68 (septuplet, 1H), 6.92 (d, 2H), 6.95 (d, 1H), 7.38 (s, 1H), 7.47 (d, 2H), 8.31 (d, 1H), 9.18 (s, 1H) [+duetero acetic acid: 3.01 (b d, 2H), 3.14 (t, 4H), 3.33 (t, 4H), 3.37 (m, 2H)]; m/z 478.

Example 26

2-{4-[4-(2-Methoxyethylsulphonyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

Sodium methoxide (40 mg 0.74 mmol) was added to 2-{4-[4-(vinylsulphonyl) piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl) pyrimidine (Example 24;300 mg 0.64 mmol) in methanol (4 ml). After stirring at room temperature for 5 hours, the reaction was evaporated. After chromatography on silica gel using methanol:DCM:EtOAc (5:47.5:47.5) and trituration with ether, the title compound was obtained as a yellow solid. NMR: 1.41 (d, 6H), 2.47 (s, 3H), 3.13 (m, 4H), 3.26 (4H alongside exchangeables), 3.37 (t, 2H), 3.67 (t, 2H), 5.69 (septuplet, 1H), 6.93 (d, 2H), 6.96 (d, 1H), 7.39 (s, 1H), 7.49 (d, 2H), 8.32 (d, 1H), 9.18 (s, 1H); m/z 500.

Example 27

2-{4-[4-(2-Hydroxyethylsulphonyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

A mixture of 2-{4-[4-(vinylsulphonyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl) pyrimidine (Example 24;260 mg 0.56 mmol) and barium hydroxide (560 mg 3.27 mmol) in water (10 ml) was heated at 65°C - 90°C over 6 hours. 1,4-dioxane (1 ml) was added after 1, 2, 3 and 5 hours. After evaporation under reduced pressure, the residue was treated with water (10 ml) and saturated sodium hydrogen carbonate solution (10 ml). The suspension was extracted with DCM (30 ml and 2x20 ml) and EtOAc (25 ml). Both extracts were washed (separately) with brine (10 ml) and dried (Na_2SO_4). The extracts were combined and evaporated. After chromatography on silica gel using methanol:DCM (4:96 to 8:92), the title compound was obtained as a yellow solid (108 mg 40%). NMR: 1.40 (d, 6H), 2.49 (s, 3H), 3.13 (m, 4H), 3.23 (t, 2H), 3.30 (m, 4H), 3.76 (q, 2H), 5.01 (t, 1H), 5.69 (septuplet, 1H), 6.93 (d, 2H), 6.96 (d, 1H), 7.39 (s, 1H), 7.48 (d, 2H), 8.31 (d, 1H), 9.18 (s, 1H), m/z 486.

Example 28

2-[4-(4-Acetylpiperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-chloropyrimidine

(2*E*)-2-Chloro-3-(dimethylamino)-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (1.68g from Method 3 - assumed 5mmol) and *N*-[4-(4-acetylpiperazin-1-yl)phenyl]guanidine (Method 2) (1.94g 6mmol) in 2-methoxyethanol (25ml) were heated under nitrogen at 110°C for 3.5 hours before evaporation under reduced pressure. The residue was purified by chromatography on silica gel with methanol:DCM (3:97 to 5:95) to give the title compound, after trituration with ether, as a foam. NMR: 1.36 (d, 6H), 2.02 (s, 3H), 2.48 (s, 3H), 3.00 (b t, 2H), 3.08 (b t, 2H), 3.56 (b q, 4H), 4.80 (septuplet, 1H), 6.90 (d, 2H), 7.21 (s, 1H), 7.47 (d, 2H), 8.50 (s, 1H), 9.48 (s, 1H); m/z 454.

Example 29

2-[4-(Piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-chloropyrimidine

The title compound was prepared from 2-[4-(4-acetylpiperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-chloropyrimidine (Example 28; 800mg) by the method of Example 20. Except that after purification by chromatography on neutral alumina, activity II eluting with methanol:DCM (3:97) the title compound was isolated as a yellow gum. Trituration with ether gave a foam (50mg 7%). NMR: 1.34 (d, 6H), 2.45 (s, 3H), 2.82 (m, 4H), 2.96 (m, 4H), 4.82 (septuplet, 1H), 6.85 (d, 2H), 7.41 (s, 1H), 7.42 (d, 2H), 8.49 (s, 1H), 9.43 (s, 1H); m/z 412.

Example 30

2-[4-(Morpholino)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-chloropyrimidine

(2*E*)-3-(Dimethylamino)-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 24 of WO 03/076436); (110mg 0.5mmol) and *N*-[4-(morpholino)phenyl]guanidine bicarbonate salt (Method 4; 170mg 0.6mmol) in dimethylacetamide (4ml) were heated for 20 minutes at 200°C in a microwave. The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with methanol:DCM (4:96 to 8:92) to give the title compound, after trituration with ether, as a solid 90mg 50%. NMR 1.42 (d, 6H), 2.48 (s, 3H), 3.06 (t, 4H), 3.75 (t, 4H), 5.71 (septuplet, 1H), 6.91 (d, 2H), 6.97 (d, 1H), 7.40 (s, 1H), 7.48 (d, 2H), 8.32 (s, 1H), 9.18 (s, 1H); m/z 379.

Preparation of Starting Materials

Method 1

N-{4-[4-(Methylsulphonyl)piperazin-1-yl]phenyl}guanidine

1-Methylsulphonyl-4-(4-nitrophenyl)piperazine [J. Med. Chem. 20 (8) 987-996 (1977)] (24g) in ethanol (250 ml) was hydrogenated over 10% Pd / carbon (2.4 g) at ambient temperature and pressure. The reaction was filtered and the catalyst and insoluble solid were washed with methanol:2N hydrochloric acid (100:100 ml). Evaporation under reduced pressure gave the aniline hydrochloride as an orange solid (19.8 g 81%). M/z: 256.

A mixture of the aniline (4.7g 16.1 mmol) and cyanamide (800 mg 19.0 mmol) in ethanol (25 ml) and 1,4-dioxane (25 ml) were heated at 90°C - 95°C for a total of 19 hours. Extra cyanamide (450 mg) and ethanol (10 ml) were added after 5.5 hours. The reaction mixture was evaporated under reduced pressure. Water (100 ml) was added to the residue before basifying with 40% sodium hydroxide (pH>11). The solid was filtered off, washed with a little cold water, dried on a filter then transferred to a beaker. The residue was triturated with acetone (50 ml), filtered and air dried to give the title compound (3.2 g 58%). NMR: 2.89 (s, 3H), 3.08 (m, 4H), 3.21 (m, 4H), 3.30 (b s, 4H), 6.73 (d, 2H), 6.73 (d, 2H); m/z: 298.

Method 2

N-[4-(4-Acetylpiperazin-1-yl)phenyl]guanidine

1-Acetyl-4-(4-nitrophenyl)piperazine [J. Med. Chem. 20 (8) 987-996 (1977)] (20.8 g) in ethanol (200 ml) was hydrogenated over 10% Pd / carbon (2.1 g) at ambient temperature and pressure. The catalyst was filtered off, washed with ethanol (500 ml) and evaporation under reduced pressure to give the aniline as a purple solid, 22g (still wet).

The aniline (5.0 g 22.8 mmol) was stirred in dry 1,4-dioxane (55 ml) and ethanol (20 ml). 4N HCl in dioxane (6.0 ml 25 mmol) was added then, after 3 to 4 minutes, cyanamide (1.6 g 38.1 mmol) and extra ethanol (4 ml) were added. The reaction was heated at 95°C for 17.5 hours then extra cyanamide (300 mg) and 4N HCl / dioxane (2 ml) were added. The reaction was continued with heating for 6 hours. After evaporation under reduced pressure, the solid was triturated with ether (2x70 ml) and air dried. The solid was dissolved in water (40 ml), slowly added saturated sodium hydrogen carbonate solution (75 ml) with stirring. After 21 hour, the solid was collected by filtration, washed with acetone (2x40 ml) and dried

under vacuum. (5.7g 77%). NMR: 2.01 (s, 3H), 2.98 (t, 2H), 3.05 (t, 2H), 2.9-3.8 (v b s, exchangeables), 3.54 (m, 4H), 6.81 (d, 2H), 6.88 (d, 2H); m/z 262.

Method 3

(2*E*)-2-Chloro-3-(dimethylamino)-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one

Benzyltrimethylammonium dichloroiodate (2.6g 7.5mmol) was added in portions to a stirred solution of (2*E*)-3-(dimethylamino)-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 24 of WO 03/076436; 1.1g 5mmol) in methanol/DCM (15/30ml) at room temperature. After 1 hour water (10ml) and DCM (20ml) were added followed after a further 30 minutes by saturated sodium hydrogen carbonate solution (20ml). The organics were separated, re-extracted the aqueous with DCM (25ml). The combined organics were washed with 5% (w/v) sodium thiosulphate solution (30 to 35ml) and brine (25ml), dried (Na_2SO_4) and evaporated to give the title compound as an oil (crude yield 1.68 g still wet). M/z 256.

Method 4

N-[4-(Morpholino)phenyl]guanidine bicarbonate salt

4-Morpholino aniline (1.78g 10mmol) and cyanamide (420mg 10mmol) were stirred in 1,4-dioxane (17.5ml). 7N HCl in 1,4-dioxane (2.5ml) was slowly added before heating at 95°C for 11 hours. The reaction mixture was evaporated under reduced pressure and the solid triturated with ether before air-drying overnight. This solid was treated with water (20ml) and stirred during slow addition of saturated aqueous sodium hydrogen carbonate solution (15ml). The solid was collected by filtration, washed with acetone (15ml) and air dried to give the title compound 2.3g 80%. NMR 2.95 (4H, m), 3.39 (exchangeables, v br s), 3.68 (4H, m), 6.68 (2H, d), 6.71 (2H, d); m/z 221.

Method 5

2-Amino-5-chloro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

A solution of 2-amino-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Method 39 of WO 03/076436; 0.5g, 2.3mmol) and N-chlorosuccinimide (0.4g, 3mmol) in acetic acid (5 ml) was stirred at 65°C under nitrogen for 2 hours. Then the reaction mixture was allowed to cool down to room temperature and the solvent was removed under vacuum. The crude was taken up in ethyl acetate and water then portions of solid potassium carbonate were added to

this stirred biphasic solution until pH 8-9 was reached. The two layers were separated, the aqueous layer was extracted once with ethyl acetate then the organics were combined, washed with brine and dried over magnesium sulphate. Removal of the solvent left a residue, which was purified on silica (methanol/DCM/ethyl acetate, from 0/50/50 to 6/47/47). Triturating the foam in diethyl ether gave a white solid, which was filtered off. (0.49g, 85%). NMR ($CDCl_3$): 1.51 (d, 6H), 2.55 (s, 3H), 4.85 (septuplet, 1H), 5.01 (b s, 2H), 7.48 (s, 1H), 8.31 (s, 1H); m/z 252 (^{35}Cl), 254 (^{37}Cl) ; m/z 250 (^{35}Cl), 252 (^{37}Cl).

Method 6

4-[*N*-(Propionyl)-*N*-(isopropyl)amino]-5-methylisoxazole

Triethylamine (1.0eq.) was added dropwise over 45mins to a solution of *N*-isopropyl-5-methylisoxazol-4-amine (Method 1 of WO 03/76436; 258g, 1.0eq.) and n-propionyl chloride (1.0eq) in dichloromethane (8.6vol.eq.) at –3°C. The reaction was then stirred at 0°C for 20mins and then left to warm to room temperature overnight. Water (10vol.eq) was added and the mixture was then stirred for 30mins. The organic layer was separated and washed with water (2 x 10vol.eq.), 2M HCl (3 x 10vol.eq.), brine (10vol.eq.), dried (magnesium sulphate), filtered and the solvent was then removed *in vacuo* from the filtrate to leave a yellow oil which crystallised on standing (330g, 91%). NMR 0.91 (3H, t), 0.95 (6H, b s), 1.9 (2H, q), 2.35 (3H, s), 4.8 (1H, septuplet), 8.61 (1H, s).

Method 7

N-[(*E*)-1-Acetyl-2-aminoethenyl]-*N*-isopropylpropanamide

4-[*N*-(Propionyl)-*N*-(isopropyl)amino]-5-methylisoxazole (Method 6; 330g, 1.0eq.) was stirred under hydrogen (1.0eq), with 10% palladium on carbon (0.1eq.) in ethanol (10vol.eq.) at 25°C overnight. The catalyst was removed by filtration and the ethanol was removed *in vacuo* to leave an off white solid (351g, 98%).This was used without further purification.

Method 8

1-Isopropy-2-ethyl-5-acetylimidazole

N-[(*E*)-1-Acetyl-2-aminoethenyl]-*N*-isopropylpropanamide (Method 7; 373g, 1.0eq.) was stirred with sodium hydroxide (1.4eq.) in ethanol (4vol.eq.). The reaction was heated to reflux (85°C) and stirred overnight. Ammonium chloride (2.0eq.) was then added and this was

stirred for 2 hours (the consistency of the reaction changed to a fine precipitate). The reaction was then allowed to cool, the solid was filtered off and discarded, and the solvent was then removed *in vacuo*. Acetone was then added to the residue, the solid was filtered off and discarded. The solvent was then removed *in vacuo*. Prep chromatography was then performed by eluting with 5% methanol / dichloromethane, to leave a brown oil (290g, 86%). NMR 1.23 (3H, t), 1.43 (6H, d), 2.40 (3H, s), 2.77 (2H, q), 5.0 (1H, b s), 7.87 (1H, s).

Method 9

5-(3-Dimethylaminoprop-2-en-1-oyl)-1-isopropyl-2-ethylimidazole

1-Isopropy-2-ethyl-5-acetylimidazole (Method 8; 290g, 1.0eq.) was stirred with dimethylformamide diethyl acetal (2.0eq.) in dimethylformamide (15vol.eq.). The reaction was heated to 130°C and stirred overnight. The reaction was allowed to cool and the solvent removed *in vacuo*. The residue was triturated with diethyl ether and the brown solid filtered off, washed with diethyl ether, this process was repeated. The filtrates were then combined and purified by prep chromatography eluting with 5% methanol / dichloromethane to give a yellow solid (223g, 59%). NMR 1.24 (3H, t), 1.46 (6H, d), 2.73 (2H, q), 2.96 (6H, b s), 5.09 (1H, septuplet), 5.56 (1H, d), 7.51 (1H, s), 7.53 (1H, d).

Method 10

4-(*N*-Butyryl-*N*-ethylamino)-5-methylisoxazole

To a stirred, ice cooled solution of 4-ethylamino-5-methylisoxazole (Method 5 of WO 03/76436; 49.6g, 305mM) and triethylamine (77.0g, 763mM, 107ml) in DCM (800ml), was slowly added a solution of n-butyryl chloride (35.5, 333mM, 35ml) in DCM (100ml). There was a moderate exotherm. The solution was allowed to warm to ambient temperature and stir for 1 hour. The reaction mixture was washed with water, 2N HCl, brine, sat. $NaHCO_3$ and brine. It was dried over anhydrous $MgSO_4$ and the solvent was evaporated to give the title compound as an oil, which crystallized to a waxy solid (45.1g, 75%). NMR (300Mz, DMS0-d6): 0.78 (t, 3H), 0.96 (t, 3H), 1.44 (sext, 2H), 1.93 (t, 2H), 2.33 (s, 3H), 3.49 (q, 2H), 8.68 (s, 1H); m/z 197.

Method 11

N-[(*E*)-1-Acetyl-2-aminoethenyl]-*N*-ethylbutanamide

A solution of 4-(*N*-butyryl-*N*-ethylamino)-5-methylisoxazole (Method 10; 45g, 230mM) in EtOH (1.5l) was hydrogenated over 10% Pd/C (11.25g) at 4 bar. The catalyst was filtered off and the solution was evaporated. The residue was triturated with ether and the crystalline intermediate was filtered off (33.94g). This was used without further purification.

Method 12

1-Ethyl-2-propyl-5-acetylimidazole

A solution of *N*-[(*E*)-1-acetyl-2-aminoethenyl]-*N*-ethylbutanamide (Method 11; 33.9g, 171mM) and NaOH (8.2g, 205mM) in EtOH (400ml) was heated under reflux for 4 hours. NH_4Cl (11.9g, 222mM) was added to the hot solution, which was allowed to cool and stir for 48 hours. The reaction mixture was filtered and the solution was evaporated. The residue was taken into ether and filtered again. The solution was evaporated to give the title compound as a yellow oil (30.55g, 74%). NMR (300Mz, DMS0-d6): 0.92 (t, 3H), 1.17 (t, 3H), 1.70 (sext, 2H), 2.37 (s,3H), 2.64 (t, 2H), 4.23 (q, 2H), 7.83 (s, 1H); m/z 181.

Method 13

5-(3-Dimethylaminoprop-2-en-1-oyl)-1-ethyl-2-propylimidazole

A solution of 1-ethyl-2-propyl-5-acetylimidazole (Method 12; 30.5g, 169mM) and dimethylformamide diethylacetal (49.7g, 338mM, 58ml) in DMF (100ml) was stirred at 130°C for 18 hours, allowing distillation of the ethanol generated. On cooling, the product crystallized from the reaction mixture and was filtered and washed with ether (20.94g). A second crop was obtained on evaporating the solvent and triturating with ether (8.8g) (29.74g, 75%). NMR (300Mz, DMS0-d6): 0.92 (t, 3H), 1.18 (t, 3H), 1.70 (sext, 2H), 2.60 (t, 2H), 2.94 (broad s, 6H), 4.30 (q, 2H), 5.56 (d, 1H), 7.50 (d, 1H), 7.56 (s,1H); m/z 236.

Example 31

The following illustrate representative pharmaceutical dosage forms containing the compound of formula **(I)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a): Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c): Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e): Injection I	**(50 mg/ml)**
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f): Injection II	**10 mg/ml**
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

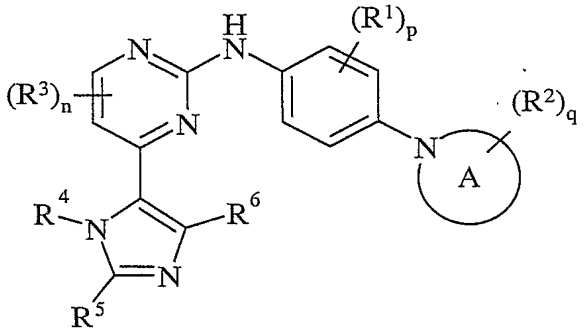
(g): Injection III	**(1mg/ml,buffered to pH6)**
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

Claims

1. A compound of formula (**I**):



(**I**)

wherein:

Ring A is a nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom; wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7;

R^1 is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkynyl;

p is 0-4; wherein the values of R^1 may be the same or different;

R^2 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; wherein R^2 independently may be optionally substituted on carbon by one or more R^8; or R^2 is -NHR^9, -NR^{10}R^{11} or -O-R^{12};

q is 0-2; wherein the values of R^2 maybe the same or different;

R^3 is halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-3}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-3}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl or *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl; wherein R^3 may be independently optionally substituted on carbon by one or more R^{13};

n is 0 to 2, wherein the values of R^3 may be the same or different;

R^4 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or a carbon-linked heterocyclyl; wherein R^4 may be optionally substituted on carbon by one or more R^{14}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15};

R^5 and **R^6** are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-8}cycloalkyl or a 4-7 membered saturated heterocyclic group; wherein R^5 and R^6 independently of each other may be optionally substituted on carbon by one or more R^{16}; and wherein if a 4-7 membered saturated heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

R^7, **R^9**, **R^{10}**, **R^{11}** and **R^{12}** are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, C_{2-6}alkynylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, carbocyclyl, heterocyclyl, carbocyclyl-R^{18}- or heterocyclyl-R^{19}-; wherein R^7, R^9, R^{10}, R^{11} and R^{12} may be independently optionally substituted on carbon by a group selected from R^{20}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by R^{21};

R^{14} and **R^{20}** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{1-6}alkyl-R^{22}-, heterocyclylC_{1-6}alkyl-R^{23}-, carbocyclyl-R^{24}- or heterocyclyl-R^{25}-; wherein R^{14} and R^{20} may be optionally substituted on carbon by one or more R^{26}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{27};

$\mathbf{R^{18}}$, $\mathbf{R^{19}}$, $\mathbf{R^{22}}$, $\mathbf{R^{23}}$, $\mathbf{R^{24}}$, $\mathbf{R^{25}}$ are independently selected from -O-, -N(R^{28})-, -C(O)-, -N(R^{29})C(O)-, -C(O)N(R^{30})-, -S(O)$_s$-, -SO_2N(R^{31})- or -N(R^{32})SO_2-; wherein $\mathbf{R^{28}}$, $\mathbf{R^{29}}$, $\mathbf{R^{30}}$, $\mathbf{R^{31}}$ and $\mathbf{R^{32}}$ are independently selected from hydrogen or C_{1-6}alkyl and **s** is 0-2;

$\mathbf{R^{15}}$, $\mathbf{R^{17}}$, $\mathbf{R^{21}}$ and $\mathbf{R^{27}}$ and are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R^{15}, R^{17}, R^{21} and R^{27} independently of each other may be optionally substituted on carbon by on or more R^{33}; and

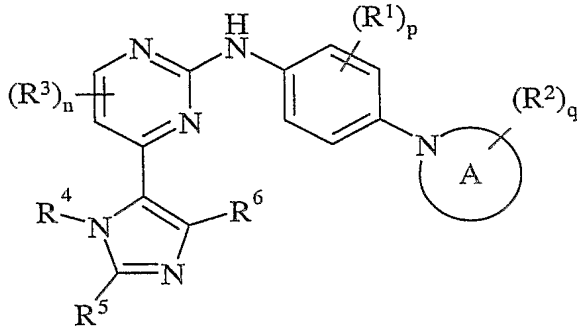
$\mathbf{R^{8}}$, $\mathbf{R^{13}}$, $\mathbf{R^{16}}$, $\mathbf{R^{26}}$ and $\mathbf{R^{33}}$ are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

ABSTRACT

TITLE: CHEMICAL COMPOUNDS

Compounds of the formula **(I)**:



(I)

wherein variable groups are as defined within and a pharmaceutically acceptable salts and *in vivo* hydrolysable esters are described. Also described are processes for their preparation and their use as medicaments, particularly medicaments for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man.